REMARKS

Claims 47-62 presently appear in this case. The previously appearing claims had been subject to a restriction requirement. No claims have been allowed. The official action of March 27, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method which is now known in the art as autoimmune neuroprotection. It has been discovered that neuronal degeneration caused by the neurodegenerative effects of disease or secondary neuronal degeneration that follows the primary neuronal damage of an injury can be reduced if steps are taken to cause T cells activated against an NS-specific antigen which, in its native state, is present at the site of neuronal degeneration, to accumulate at the site of neuronal degeneration. The mere presence of these activated T cells at the site of injury causes a cytokine response that has a significant effect in reducing the neuronal degeneration. The preferred methods of causing the T cells to accumulate at the site of injury is to either administer T cells activated against an NS-specific antigen, which in its native state is present at the site of the injury, or to administer the antigen itself in such a way as to cause a T cell response such that T cells become

activated against the NS-specific antigen which is present at the site of neuronal degeneration.

The interview among examiners, Bunner and Kunz, the inventor, Prof. Michal Schwartz, and the undersigned attorney, which interview was also attended by examiners Turner, Kemmerer, and Nichols, on June 26, 2003, is hereby gratefully acknowledged. In this interview, Prof. Schwartz presented a slide presentation explaining the work of her laboratory that resulted in the present invention and the subsequent work which has been done in proving broad applicability of the present invention. This work has been published in prestigious journals, copies of which are being made of record herewith. Claim wording that might appropriately claim the full breadth of this invention without reading on the prior art and in full compliance with 35 USC 112 was discussed at the interview. While no agreements were reached, it is believed that the examiners now have a better understanding of the present invention, and that in additional discussions, the examiners can help applicants in appropriate wording of the claims in order to obtain appropriate protection for this important and novel advance in the art.

All of the claims in this application have now been deleted in favor of new claims 47-62. The new claims submitted herewith attempt to adopt the language that was

discussed at the interview. If this language is not considered to put this case into condition for allowance, it is respectfully requested that the examiner contact the undersigned to schedule a further interview to discuss language for this case that might be acceptable.

Support for the language of new claims 47 and 55 may be found in the specification. For example, the paragraph bridging pages 37 and 38 discloses that the invention may be used to ameliorate the effects of disease that result in a degenerative process (page 37, lines 13-15). Page 37, lines 8-11, discloses the inhibition of secondary degeneration that may otherwise follow primary NS injury. With respect to claim 55, note the "Field of the Invention" on page 1, which states that the present invention relates to methods to "ameliorate the effects of injury or disease of the nervous system". Support for the definition of NS-specific antigen appears at page 8, lines 3-6, where it states:

> "NS-specific antigen" as used herein refers to an antigen that specifically activates T cells such that following activation the activated T cells accumulate at a site of injury or disease in the NS of the patient.

See also the paragraph bridging pages 30 and 31. Page 31, lines 10-12, discloses that the NS-specific antigen is one which in its native state is in tissue at the site of CNS injury or disease. The immunogenic and cryptic peptides are

disclosed in the first paragraph on page 33. Accordingly, it is submitted that the newly presented claims are fully supported by the written description of the present specification.

It should be noted that the present claims specify that when the individual in need has an autoimmune disease, the NS-specific antigen is not the autoimmune antigen of that disease, and when the individual in need has a neoplasm, the NS-specific antigen is one that does not appear in the antigen. This language is supported in the paragraph bridging pages 38 and 39 of the present specification. The first proviso is inserted so as to exclude embodiments that exacerbate an autoimmune disease. The second proviso is added so that the claim will not read on prior art antineoplastic immunotherapy.

The examiner has deemed the previous restriction requirement to be proper and has made it final. It is urged, however, that new claims 47 and 55 are linking claims that appropriately claim the full breadth of the present invention. The main step of both claims is causing T cells activated against an NS-specific antigen, which in its native state is present at the site of neuronal degeneration, to accumulate at the site of neuronal degeneration in the individual in need, thereby reducing neuronal degeneration at that site or

ameliorating the effects of the injury or disease at that site. This is generic to preferred methods of active and passive administration of such T cells as claimed in claims 48 and 49 and claims 56 and 57. Furthermore, as was explained in the interview, the effect of the invention is the same whether treating secondary degeneration caused by an injury or the degeneration caused by a disease. Accordingly, it is again respectfully requested that the restriction requirement be reconsidered and withdrawn in view of the presence of the linking claims submitted hereby.

The examiner has objected to the specification regarding a more descriptive title. The title has been amended to read:

> A METHOD FOR REDUCING NEURONAL DEGENERATION SO AS TO AMELIORATE THE EFFECTS OF INJURY OR DISEASE

It is believed that this title is now descriptive of the presently claimed invention. Accordingly, reconsideration and withdrawal of the objection to the disclosure is respectfully urged.

The examiner has objected to claims 1, 2, 19 and 38-41 as reciting non-elected groups and species.

These claims have now all been deleted. It is believed that the restriction requirement is now moot in view of the presentation of new claims.

Claims 1-2, 38-41 and 43 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 16 of co-pending application number 09/218,277.

As neither the present application nor the '277 application have allowable claims, it is respectfully requested that this provisional rejection be held in abeyance until allowable subject matter is indicated in one or the other of the applications. At that time a decision can be made whether to maintain a line of distinction between the claims, to abandon one of these applications, or to file a terminal disclaimer. Accordingly, it is requested that this rejection be held in abeyance, in accordance with 37 CFR §1.111(b), until allowable subject matter is indicated in accordance with 37 CFR §1.111(b).

Claims 1-2, 4-8, 19, 38-41 and 43 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for (i) a method of reducing secondary neuronal degeneration in the CNS or PNS of an individual suffering from the degenerative effects of a spinal cord injury or blunt trauma comprising intraperitoneally administering to an individual in need thereof a composition consisting of activated T cells sensitized to MBP, wherein the MBP-activated T cells accumulate at the site of injury or

blunt trauma to reduce secondary neuronal degeneration, does not reasonably provide enablement for a method for reducing neuronal degeneration in the CNS or PNS for ameliorating the effects of injury commensurate in scope with the claims. This rejection is respectfully traversed.

Prof. Schwartz made a comprehensive presentation explaining why predictions made in the present specification have been proved to be accurate. So many embodiments have been successfully tested that it would no longer be unexpected that the full scope of the present invention would work as disclosed. Furthermore, it would not take undue experimentation to make and use the invention with respect to other NS-specific peptides or other neurodegenerative diseases or injuries.

Attached hereto are the following thirty-eight references from the laboratory of the present inventors relating to the present invention as well as to related improvements that are based on the same concept:

> YOLES et al., "Degeneration of Spared Axons Following Partial White Matter Lesion: Implications for Optic Nerve Neuropathies", Experimental Neurology, 153:1-7 (1998)
>
> MOALEM et al., "Autoimmune T Cells Protect Neurons from Secondary Degeneration after Central Nervous System Axotomy", Nature Medicine, 5:49-55 (1999)

SCHWARTZ et al., "Innate and Adaptive Immune Responses Can Be Beneficial for CNS Repair", TINS, 22:295-299 (1999)

SCHWARTZ, "Vaccination for T Cell-Mediated Neuroprotection: Dream or Reality?", Drug Development Research, 50:223-225 (2000)

HAUBEN et al., "Autoimmune T Cells as Potential Neuroprotective Therapy for Spinal Cord Injury", The Lancet, 354:286-287 (2000)

SCHWARTZ et al., "Neuroprotection: A New Treatment Modality for Glaucoma?", Current Opinion in Ophthalmology, 11:107-111 (2000)

KIPNIS et al., "T Cell Immunity to Copolymer 1 Confers Neuroprotection on the Damaged Optic Nerve: Possible Therapy for Optic Neuropathies", PNAS, 97:7446-7451 (2000)

MOALEM et al., "Autoimmune T Cells Retard the Loss of Function in Injured Rat Optic Nerves", Journal of Neuroimmunology, 106:189-197 (2000)

HAUBEN et al., "Passive or Active Immunization with Myelin Basic Protein Promotes Recovery from Spinal Cord Contusion", The Journal of Neuroscience, 20:6421-6430 (2000)

MOALEM et al., "Production of Neurotrophins by Activated T Cells: Implications for Neuroprotective Autoimmunity", Journal of Autoimmunity, 15:331-345 (2000)

SCHWATRZ, "T Cell Mediated Neuroprotection is a Physiological Response to Central nervous System Insults", J Mol Med, 78:594-597 (2001)

FISHER et al., "Vaccination for Neuroprotection in the Mouse Optic Nerve: Implications for Optic Neuropathies", The Journal of Neuroscience, 21:136-142 (2001)

SCHWARTZ et al., "Beneficial Immune Activity after CNS Injury: Prospects for

Vaccination", Journal of Neuroimmunology, 113:185-192 (2001)

BUTOVSKY et al., "Morphological Aspects of Spinal Cord Autoimmune Neuroprotection: Colocalization of T Cells with B7-2 (CD86) and prevention of Cyst Formation", The FASEB Journal, express article 10.1096/fj.00-0550fje, published online February 26, 2001

SCHORI et al., "Vaccination for Protection of Retinal Ganglion Cells Against Death from Glutamate Cytotoxicity and Ocular Hypertension: Implications for Glaucoma", PNAS, 98:3398-3403 (2001)

YOLES et al., "Self-Protection Mechanism Awakened by Glutamate in Retinal Ganglion Cells", Journal of Neurotrauma, 18:339-349 (2001)

YOLES et al., "Protective Autoimmunity Is a Physiological Response to CNS Trauma", The Journal of Neuroscience, 21:3740-3748 (2001)

SCHWARTZ et al., "Protective Autoimmunity: Regulation and Prospects for Vaccination after Brain and Spinal Cord Injuries", TENDS in Molecular Medicine, 7:252-258 (2001)

KIPNIS et al., "Neuronal Survival after CNS Insult Is Determined by a Genetically Encoded Autoimmune Response", The Journal of Neurosciences, 21:4564-4571 (2001)

HAUBEN et al., "Posttraumatic Therapeutic Vaccination with Modified Myelin Self-Antigen Prevents Complete Paralysis While Avoiding Autoimmune Disease", The Journal of Clinical Investigation, 108:591-599 (2001)

FISHER et al., "Increased Post-traumatic Survival of neurons in IL-6-Knockout Mice on a background of EAE Susceptibility", Journal of Neuroimmunology, 119:1-9 (2001)

SCHORI et al., "T-Cell-Based Immunity Counteracts the Potential Toxicity of Glutamate in the Central Nervous System",

Journal of Neuroimmunology, 119:199-204 (2001)

HAUBEN et al., "Vaccination with a Nogo-A-Derived Peptide after Incomplete Spinal-Cord Injury Promotes Recovery Via a T-Cell-Mediated Neuroprotective Response: Comparison with Other Myelin Antigens", PNAS, 98:15173-15178 (2001)

SCHWARTZ et al., "Differing Views on Spinal Cord Repair", Science, 296:1400 (2002)

KIPNIS et al., "Dual Action of Glatiramer Acetate (Cop-1) in the Treatment of CNS Autoimmune and Neurodegenerative Disorders", TRENDS in Molecular Medicine, 8:319-323 (2002)

SCHORI et al., "Immune-Related Mechanisms Participating in Resistance and Susceptibility to Glutamate Toxicity", European Journal of Neuroscience, 16:557-564 (2002)

BAROUCH et al., "Autoreactive T Cells Induce Neurotrophin Production by Immune and Neural Cells in Injured Rat Optic Nerve: Implications for Protective Autoimmunity", The FASEB Journal, 16:1304-1306 (2002)

KIPNIS et al., "Myelin Specific Th1 Cells Are Necessary for Post-Traumatic Protective Autoimmunity", Journal of Neuroimmunology, 130:78-85 (2002)

SCHORI et al., "Severe immunodeficiency Has Opposite Effects on Neuronal Survival in Glutamate-Susceptible and -Resistant Mice: Adverse Effect of B Cells", The Journal of Immunology, 169:2861-2865 (2002)

SCHWARTZ et al., "Multiple Sclerosis as a By-Product of the Failure to Substain Protective Autoimmunity: A Paradigm Shift", The Neuroscientist, 8:405-413 (2002)

HAUBEN et al., "Sexual Dimorphism in the Spontaneous Recovery from Spinal Cord

Injury: A Gender Gap in beneficial Autoimmunity?", European Journal of Neuroscience, 16:1731-1740 (2002)

MIZRAHI et al., "The Tissue-Specific Self-Pathogen Is the Protective Self-Antigen: The Case of Uveitis", J Immunol, 169:5971-5977 (2002)

KIPNIS et al., "Neuroprotective Autoimmunity: Naturally Occurring $CD4^+CD25^+$ Regulatory T Cells Suppress the Ability to Withstand Injury to the Central Nervous System", PNAS, 99:15620-15625 2002)

SCHWARTZ et al., Autoimmunity on Alert: Naturally Occurring Regulatory $CD4^+CD25^+$ T Cells as Part of the Evolutionary Compromise Between a 'Need' and a 'Risk", TRENDS in Immunology, 23:530-534 (2002)

HAUBEN et al., "Therapeutic vaccination for Spinal Cord Injury: Helping the Body to Cure Itself", TRENDS in Pharmacological Sciences, 24: 7-12 (2003)

SCHWARTZ, "Macrophages and Microglia in Central Nervous System Injury: Are They Helpful or Harmful?", Journal of Cerebral Blood Flow & Metabolism, 23:358-394 (2003)

ANGELOV et al., "Therapeutic Vaccine for Acute and Chronic Motor Neuron Diseases: Implications for Amyotrophc Lateral Sclerosis", PNAS, 100:4790-4795 (2003)

SCHWARTZ et al., "Protective Autoimmunity Against the Enemy Within: Fighting Glutamate Toxicity", Trends Neurosci, 26:297-302 (2003)

The basic paper is Moalem et al, Nature (1999).

Halben, J. Neurosci. (2000) expands the original work in the optic nerve to spinal cord contusion, including both active and passive administration. This proves the concept that the

same active T cells work in radically different sites. Fisher et al, J. Neurosci. (2001), disclose active and passive vaccination to raise T cells specific to various NS-specific proteins. Butovsky et al, FASEB J (2001), show a proof of mechanism establishing that T cells get to the site of the lesion in the spinal cord. Schori et al, PNAS (2001), is an important paper relating to glutamate and glaucoma, establishing that COP 1 works where there is no myelin and MBP does not work. Yoles et al, J. Neurosci. (2001), shows the beneficial aspect of passive transfer of T cells. Hauben et al, J.C.I. (2001), disclose experiments that altered peptides work in order to obtain the benefit of neuroprotection. It should be understood that this paper won an award as one of the ten leading papers of the year for this journal. Hauben et al, PNAS (2001), shows active and passive vaccination with Nogo A. Misrachi et al, J. Immunol. (2002), is important in showing that the specificity of the antigen for beneficial autoimmunity is determined by the site and not by the type of insult. Angelov et al, PNAS (2003), shows the operability of the present invention in the PNS.

It is urged that these papers establish for the record what Prof. Schwartz was able to explain at the interview. In light of all the experiments that have been done with respect to this invention since the effective filing

date of the present application, the full scope of the present invention would be expected to be operable. There is no reason to believe that undue experimentation would be involved in order to make and use the full scope of the present invention. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 38 and 39 have been rejected under 35 USC 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The examiner states that it is inappropriate to read limitations in the specification into the claims, as the claims must independently define the invention for which the patent protection is sought. The examiner states that the claims do not recite a step which causes the NS-specific activated T cells to accumulate at the sight of neuronal degeneration. This rejection is again respectfully traversed.

Claims 38 and 39 have now been deleted. New claims 47 and 55 have as their main step "causing T cells activated against a nervous system (NS) specific antigen ... to accumulate at the sight of neuronal degeneration in the individual in need ...." Claim 48 specifies that the T cells are caused to accumulate at the site of neuronal degeneration by administering an effective amount of NS-specific antigen, and claim 49 specifies that the activated T cells are caused

to accumulate at the site of neuronal degeneration by administering an effective amount of T cells. One does not look to the claims to find out how to practice the invention they define, but to the specification. See *In re Johnson* 194 USPQ 187, 195 (CCPA 1977). It is a function of the claims to specify what applicant considers to be the invention.

No essential step is omitted, as the only essential step is causing the T cells to accumulate at the site of neuronal degeneration, as was explained in detail in the interview. Certainly the administration of NS-specific activated T cells is not an essential step for causing T cells to accumulate at the site of injury. It is not essential because the T cells can be caused to accumulate at the sight of injury by administration of antigen in such a way as to cause T cells to accumulate at the site of injury. No essential step has been omitted. Nothing else is needed in order to reduce neuronal degeneration caused by the neurodegenerative effects of disease or to reduce secondary neuronal degeneration that follows the primary neuronal damage of an injury other than causing T cells to accumulate at the site of neuronal degeneration. Claim 49, which specifies that activated T cells are administered, does not add a step to claim 47, but further defines the causing step. Breadth is not tantamount to indefiniteness. See *Ex parte Clark*, 174

USPQ 40, 42 (Bd. App. 1971). Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record, and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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